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<p>(54) Title: NOVEL BENZOPYRIDO PIPERIDYLIDENE COMPOUNDS, COMPOSITIONS, METHODS OF MANUFACTURE AND METHODS OF USE</p> <p style="text-align: center;"> (I) </p> <p>(57) Abstract</p> <p>Disclosed is a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein R represents H or a halogen atom selected from the group consisting of: Cl, Br, F, and I. Preferably R represents Cl. Also disclosed is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Further disclosed is a method of treating asthma, allergy and/or inflammation comprising administering to a mammal in need of such treatment an anti-asthmatic, anti-allergic and/or an anti-inflammatory, respectively, effective amount of a compound of formula (I).</p>			

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**NOVEL BENZOPYRIDO PIPERIDYLIDENE COMPOUNDS,
COMPOSITIONS, METHODS OF MANUFACTURE AND
METHODS OF USE**

REFERENCE TO RELATED APPLICATION

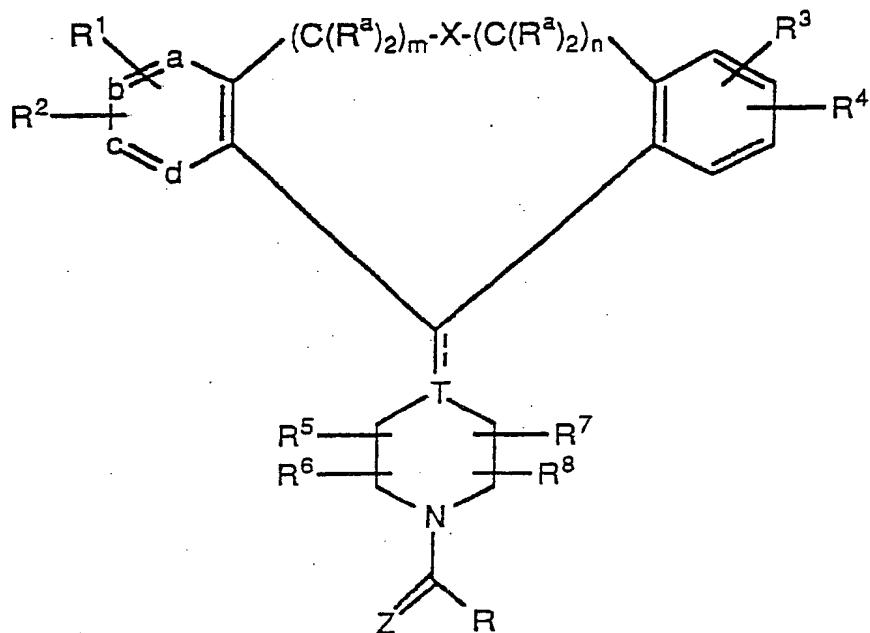
15 This application is related to International Publication Number WO 89/10369 which published on November 2, 1989 on International Application Number PCT/US89/01688 which was filed on April 26, 1989 and which has priority to U.S. Application Serial Number 187, 604 which was filed April 28, 1988, the disclosure of which is incorporated herein by reference thereto.

20 BACKGROUND OF THE INVENTION

International Publication Number WO 89/10369 discloses compounds of the formula:

25

- 2 -



wherein:

one of a, b, c and d represents nitrogen or $-NR^{11}-$, wherein

5 R^{11} is O^- , $-CH_3$ or $-(CH_2)_pCO_2H$ wherein p is 1 to 3, and the remaining a, b, c and d groups are CH which may be substituted with R^1 or R^2 ;
 R^1 or R^2 may be the same or different and each independently represents halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-S(O)_eR^{12}$ wherein e is 0, 1, or 2, $-N(R^{10})_2$, $-NO_2$, SH, CN, $-OC(O)R^{10}$, $-CO_2R^{10}$,
10 $-OCO_2R^{12}$, $-NR^{10}C(O)R^{10}$, alkyl, alkenyl or alkynyl, which alkyl or alkenyl groups may be substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$, or R^1 and R^2 may together form a benzene ring fused to the pyridine ring;
 R^{10} represents H, alkyl or aryl;
 R^{12} represents alkyl or aryl;

15 R^3 and R^4 may be the same or different and each independently represents H or any of the substituents of R^1 and R^2 , or R^3 and R^4 may be taken together to represent a saturated or unsaturated C_5 to C_7 ring fused to the benzene ring;
 R^5 , R^6 , R^7 , and R^8 each independently represents H, $-CF_3$,

20 $-CO_2R^{10}$, $-C(O)R^{10}$, alkyl or aryl, which alkyl or aryl may be substituted with $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, $-C(O)R^{10}$, $-OC(O)R^{12}$, $-CO_2R^{10}$ and

- 3 -

-OPO₃(R¹⁰)₂, or one of R⁵, R⁶, R⁷, and R⁸ may be taken in combination with R as defined below to represent -(CH₂)_r wherein r is 1 to 4, said combination being optionally substituted with lower alkyl, lower alkoxy, -CF₃ or aryl, or R⁵ may be combined with R⁶ to represent =O or =S,

5 and/or R⁷ may be combined with R⁸ to represent =O or =S;

T represents carbon or nitrogen, with the dotted line attached to T representing an optional double bond when T is carbon;

m and n are integers 0, 1, 2, or 3, such that the sum of m plus n equals 0 to 3;

10 when m plus n equals 1, X represents -O-, -S(O)_e- wherein e is 0, 1 or 2, -NR¹⁰-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, C(S)NR¹⁰-, -NR¹⁰C(S)-, -C(O)₂- or -O₂C-, wherein R¹⁰ is as defined above;

when m plus n equals 2, X represents -O-, -S(O)_e wherein e is 0, 1 or 2, or -NR¹⁰-,

15 when m plus n represents 0, X can be any substituent for m plus n equalling 1 and X can also be a direct bond, cyclopropylene or propenylene;

when m plus n equals 3 then X equals a direct bond;

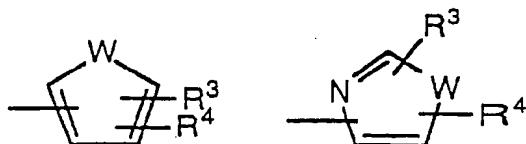
each R^a may be the same or different, and each

20 independently represents H, lower alkyl or phenyl;

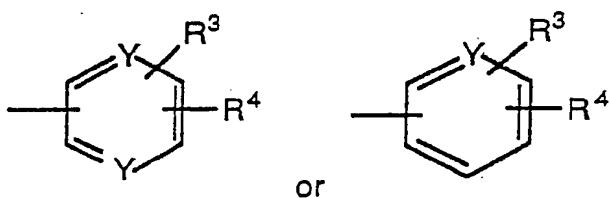
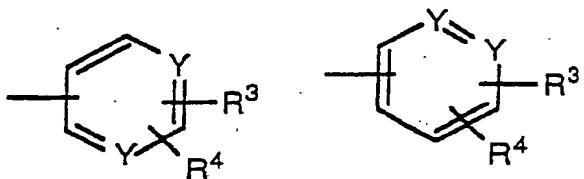
Z represents =O, =S or =NR¹³ with R¹³ equal to R¹⁰ or -CN, wherein R¹⁰ is as defined above, such that

(a) when Z is O, R may be taken in combination with R⁵, R⁶, R⁷ or R⁸ as defined above, or R

25 represents H, alkyl, aryl, -SR¹², -N(R¹⁰)₂, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents heterocycloalkyl,



- 4 -



5 wherein R³ and R⁴ are as previously defined, and W
is O, S or NR¹⁰, and wherein Y is N or NR¹¹,

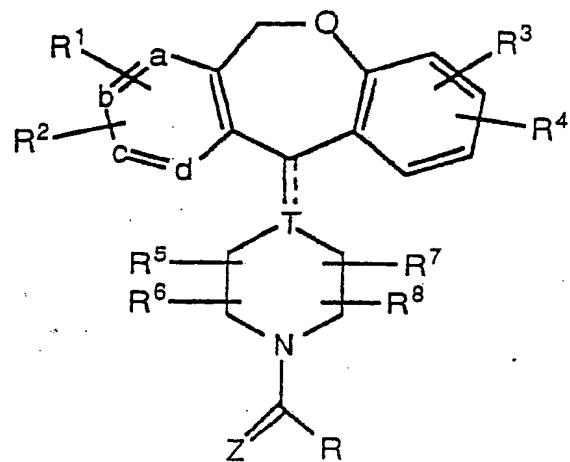
10 said cycloalkyl, alkyl, alkenyl and alkynyl being optionally substituted with from 1-3 groups selected from halo, -CON(R¹⁰)₂, aryl, -CO₂R¹⁰, -OR¹⁴, -SR¹⁴, -N(R¹⁰)₂, -N(R¹⁰)CO₂R¹⁰, -COR¹⁴, -NO₂ or -D, wherein -D and R¹⁰ are as defined above and R¹⁴ represents R¹⁰, -(CH₂)_rOR¹⁰ or -(CH₂)_qCO₂R¹⁰ wherein r is 1 to 4, q is 0 to 4; said alkenyl and alkynyl R groups not containing -OH, -SH, or -N(R¹⁰)₂ on a carbon in a double or triple bond respectively; and

15 (b) when Z represents =S, R represents in addition to those R groups above, aryloxy or alkoxy; and

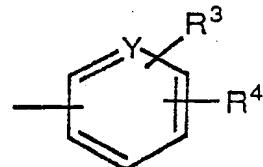
(c) where Z represents $=NR^{13}$, R represents H, alkyl, aryl, $N(R^{10})_2$, cycloalkyl, alkenyl or alkynyl.

WO 89/10369 generically discloses compounds which can
20 have the structure:

- 5 -



wherein Z can be O and R can be:



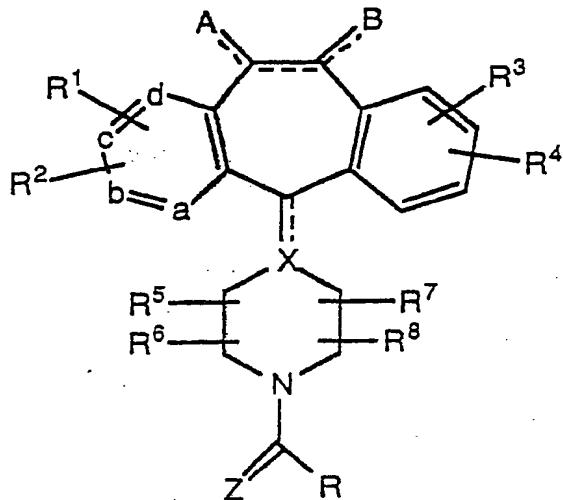
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wherein Y can be NR¹¹ and R¹¹ can be -O⁻; however, no specific compounds are disclosed with this structure.

U.S. 4,826,853 issued to Piwinski et al. on May 2, 1989 is the priority document for WO 88/03138 which published on May 5, 1988.

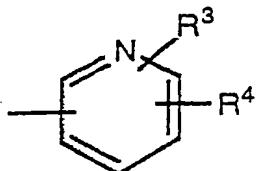
10 WO 88/03138 discloses compounds of the formula:

- 6 -



The various substituent groups are described on pages 2 to 3 of WO 88/03138. For example, X represents N or C, which C may contain an optional double bond to carbon atom 11; the dotted line between carbon atoms 5 and 6 represents an optional double bond and when no double bond is present A and B can be, amongst other groups, H₂; Z can be, amongst other atoms, O and R can be, amongst other substituents, alkyl or

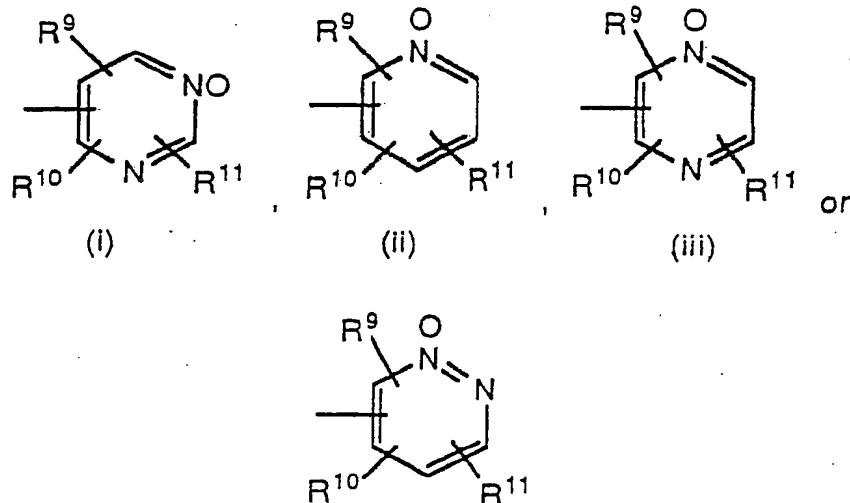
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WO 90/13548 published on November 15, 1990 on PCT/US90/02251 which was filed on April 30, 1990 and claims priority to U.S. Application Serial No. 345,604 filed May 1, 1989 discloses 15 compounds similar in structure to the compounds disclosed in WO 88/03138 with the difference being that the R group represents an N-oxide heterocyclic group of the formula (i), (ii), (iii), or (iv):

- 7 -



5

wherein R⁹, R¹⁰, and R¹¹ can be, amongst other groups, H.

Copending U.S. Application Serial No. 625,261 filed on December 10, 1990 is related to WO 90/13548.

10 The following references have disclosed oxygen or sulfur in the bridgehead of the three ring portion of the molecule:

- (1) Canadian Application 780,443, published in the name of Sandoz Patents Ltd.;
- (2) Eire 17764, published April 5, 1964 in the name of Sandoz Patents Ltd.;
- (3) European Patent Application 81816337.6, Sandoz A.G., published March 10, 1982;
- (4) Belgian Application 638,971, Sandoz S.A., published April 21, 1964;
- (5) Belgian Application 644,121, Sandoz S.A., 20 published August 20, 1964;
- (6) U.S. Patent 4,609,664, issued to Hasspacher on September 2, 1986;
- (7) U.S. Patent 3,966,944, issued to Carter on June 29, 1976;
- (8) U.S. Patent 3,803,153, issued to Villani on April 9, 1974;

- 8 -

(9) U.S. Patent 3,803,154, issued to Drukker on April 9, 1974; and

(10) U.S. Patent 3,325,501, issued to Ettinsen et al. on June 13, 1967.

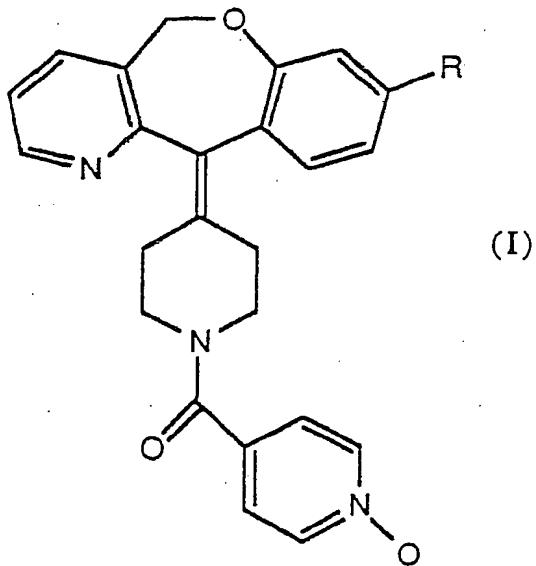
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None of references (1) to (10) above disclose substitution on the piperidylidene nitrogen similar to that described below for the compounds of this invention.

10 SUMMARY OF THE INVENTION

Surprisingly and unexpectedly it has been discovered that a specific group of compounds, generically disclosed but not specifically disclosed in WO 89/10369, have a highly desirable combination of anti-PAF and anti-histamine activity. This specific group of compounds, 15 represented by Formula I below, are in general more equipotent in their anti-PAF to anti-histamine activity than known compounds, and this activity has a longer duration.

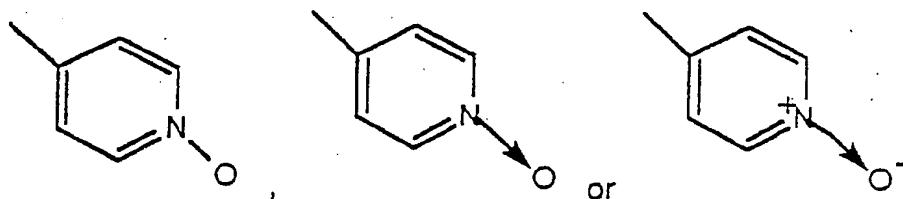
This invention provides compounds represented by
20 Formula I:



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or a pharmaceutically acceptable salt or solvate thereof, wherein R represents H or a halogen atom selected from the group consisting of: Cl, Br, F, and I. Preferably R represents Cl.

5 Those skilled in the art will appreciate that the N-oxide heterocyclic ring may be equally represented as:



10 This invention also provides a pharmaceutical composition comprising a compound represented by Formula I and a pharmaceutically acceptable carrier.

15 This invention further provides a method of treating asthma, allergy and/or inflammation in a mammal, preferably a human, in need of such treatment, said method comprising administering an anti-asthmatic, anti-allergic and/or anti-inflammatory effective amount, respectively, of a compound of Formula I. Preferably the compound is administered as a pharmaceutical composition of this invention.

20 DETAILED DESCRIPTION OF THE INVENTION

Certain compounds of the invention may exist in different isomeric forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

25 The compounds of the invention of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

30 Compounds of the invention are basic in nature, i.e., all compounds possess a pyridine ring. Hence, they may form

- 10 -

pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atom may form salts with strong acid. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, fumaric, maleic, methanesulfonic and other mineral and

5 carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium

10 carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

15 All such base salts (e.g. pyridinyl nitrogen salts) are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

20 The following processes may be employed to produce compounds of Formula I.

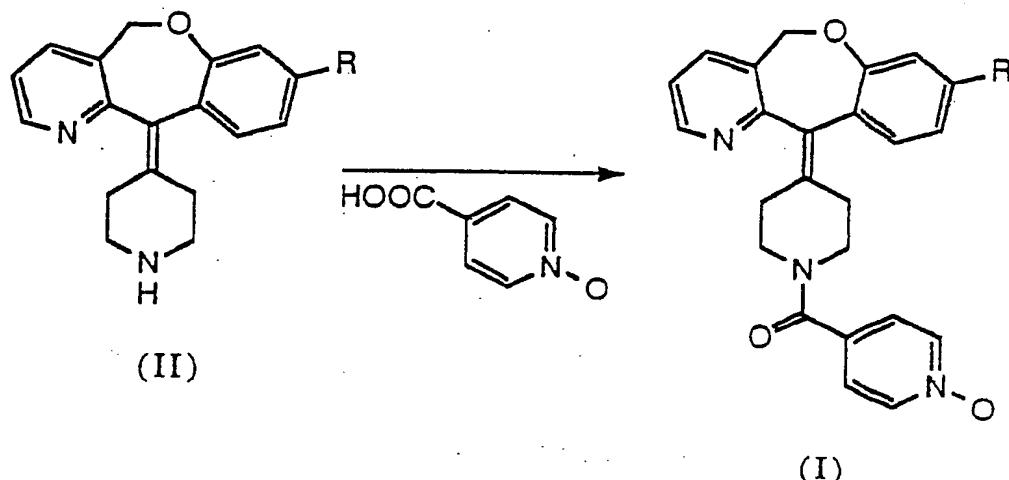
Processes A To C For The Preparation Of Compounds Of Formula I

25

Process A

In the preferred method, a compound of Formula II (wherein R is as defined in Formula I) can be coupled with iso nicotinic acid N-oxide in the presence of a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC), N,N'-dicyclohexylcarbodiimide (DCC) or N,N'-carbonyl-diimidazole (CDI) to produce compounds of Formula I:

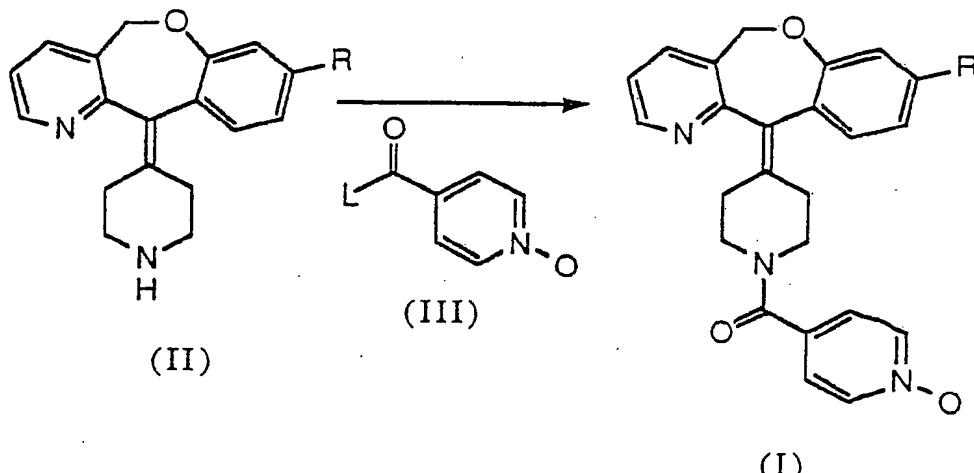
- 11 -



5 The reaction is usually conducted in an inert solvent such as tetrahydrofuran or methylene chloride at a temperature between 0°C and reflux, usually at room temperature. When the coupling agent is DCC or DEC, the reaction is preferably run in the presence of 1-hydroxybenzotriazole (HOBT).

10

A compound of Formula II may also be reacted with a compound of Formula III in the presence of a base to produce compounds Formula I:



15

(I)

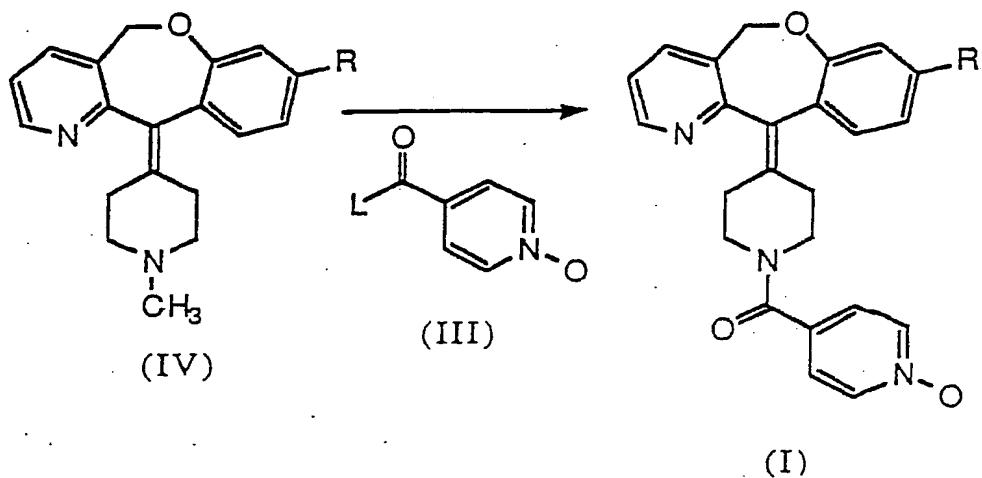
- 12 -

Representative examples of bases are pyridine and triethylamine. L designates a suitable leaving group. For example, a compound of Formula III may be an acyl halide (e.g., L is Cl), in which case

5 compound III can be generated from the corresponding carboxylic acid using oxalyl chloride.

Process C

10 Compounds of Formula I may also be prepared by reacting a compound of Formula IV with a compound of Formula III:



15 Preferably this reaction may be run in the presence of a suitable nucleophile (e.g., LiI, and the like) in an inert solvent (e.g., toluene, dioxane or xylenes). A suitable base, such as triethylamine may be added, and heating may usually be required. Typically, a temperature ranging from about 50 to about 150°C (preferably about 100 to about 20 120°C) may be utilized depending on the boiling point of the solvent.

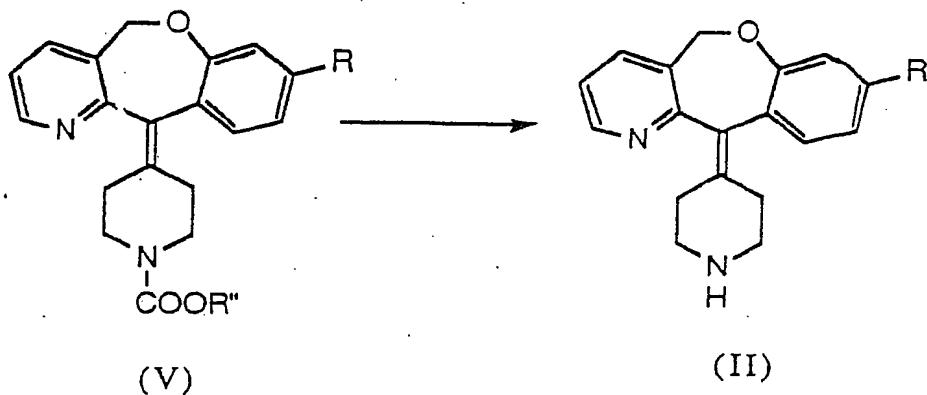
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Preparation Of Intermediate Compounds Used To Prepare Compounds of Formula I By Above Processes A To C.

Preparation of a compound of Formula II.

5

Compounds of the general Formula II can be prepared by cleaving a carbamate group (COOR'' wherein R'' is an alkyl group, such as ethyl, or an aryl group, such as phenyl) from the corresponding carbamates of Formula V. This can be accomplished by a variety of methods including acid hydrolysis (e.g., HCl) or base hydrolysis (e.g., KOH) as long as R'' is a group which does not prevent the cleavage reaction (e.g., R'' can be an alkyl group such as methyl or ethyl). Alternatively, depending on the nature of R'' , as determined by one who is skilled in the art, a compound of Formula V may be treated with an organometallic reagent (e.g., CH_3Li wherein R'' is an alkyl group such as ethyl) or a reductive reagent (e.g., Zn in acid where R'' is 2,2,2-trichloroethyl) in order to produce a compound of Formula II.



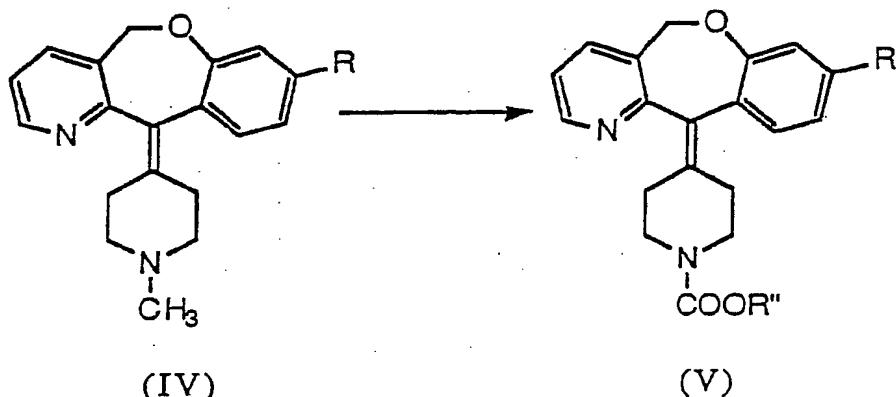
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Preparation of a compound of Formula V.

Compounds of Formula V can be prepared from the corresponding N-methyl compounds of Formula IV by treating compounds of Formula IV with a suitable chlorocarbamate containing

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R" (e.g., CICOOR"). The reaction can usually be carried out at an elevated temperature (e.g., about 70 to about 100°C) by heating a compound of Formula IV in an inert solvent, such as toluene, in the presence of the chlorocarbamate and optionally with a base such as triethylamine. This procedure is described for similar compounds in U.S. 4,282,233 and 4,335,036, the disclosures of each being incorporated herein by reference thereto.



10

Preparation of a compound of Formula VI and VII.

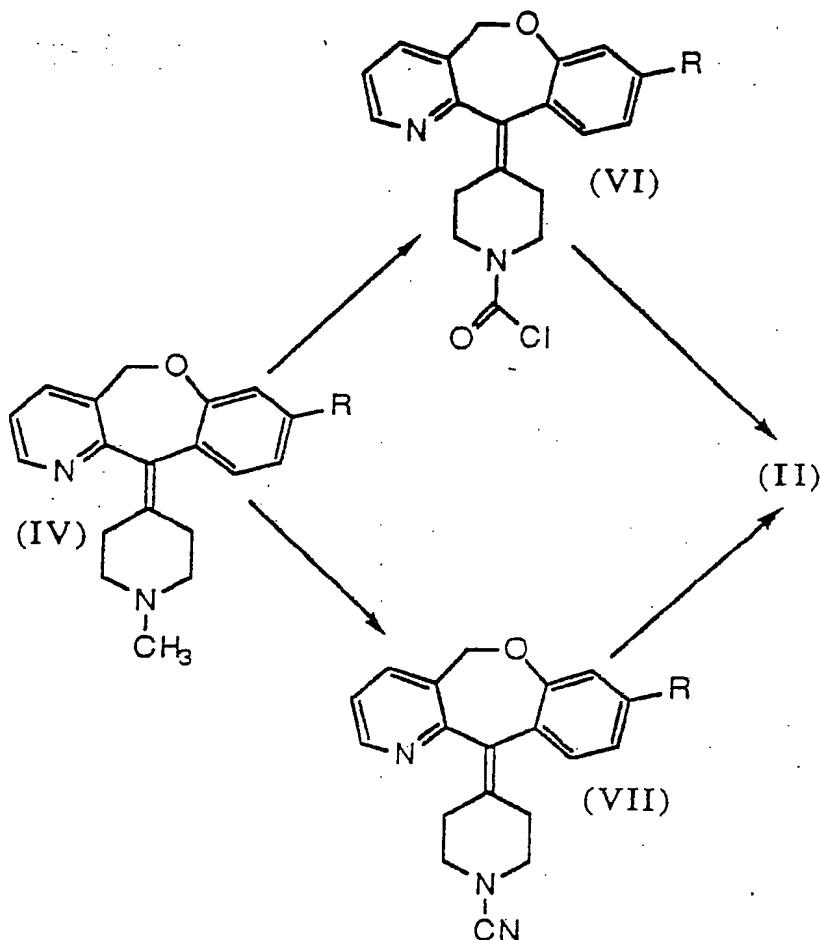
Preparation of a compound of Formula II from compounds of Formula VI and VII.

15 Those skilled in the art will appreciate that there are other methods for converting a compound of Formula IV to a compound of Formula II. For example, treatment of a compound of Formula IV with phosgene to produce a compound of the Formula VI followed by hydrolysis with aqueous acid may produce compounds of Formula II.

20 Alternatively, treatment of a compound of Formula IV with cyanogen bromide (i.e., BrCN) via Von Braun reaction conditions would provide a nitrile of Formula VII as illustrated below. Subsequent hydrolysis of the nitrile of Formula VII under either aqueous basic or aqueous acidic conditions would produce a compound of Formula II.

25

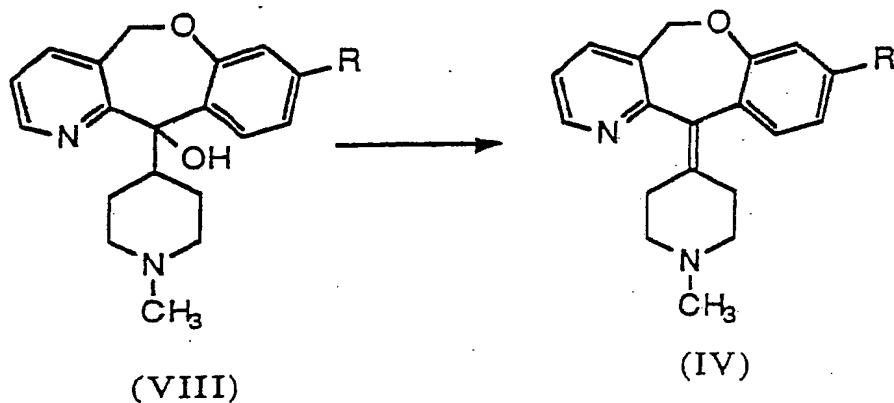
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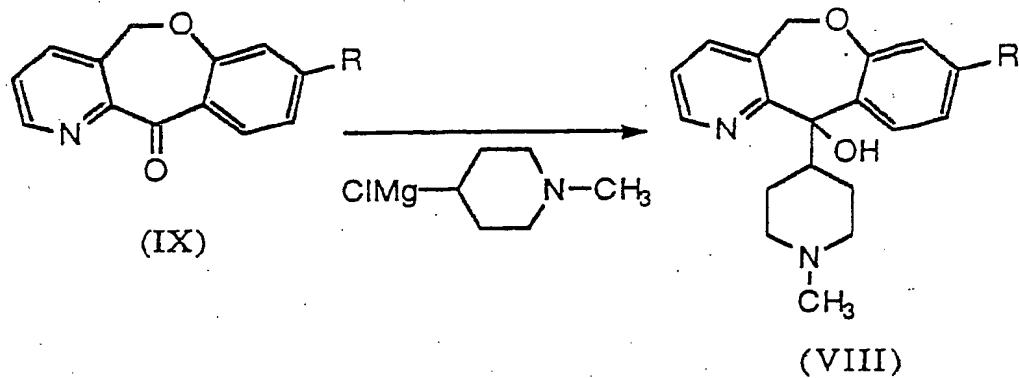
Preparation of compounds of Formula IV, method 1 steps (a)-(e).

5 (a) Compounds of Formula IV can be prepared from a corresponding alcohol of Formula VIII by using either acidic or basic conditions in accordance with methods well known in the art. For example, treatment of a compound of Formula VIII with trifluoromethanesulfonic acid and heating (about 40 to about 60°C) the
 10 mixture results in dehydration of the alcohol to produce the olefin of Formula IV. Other acids such as polyphosphoric acid or sulfuric acid may also be employed.

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(b) The alcohol of Formula VIII can be prepared via the treatment of a ketone of Formula IX with the Grignard reagent derived from N-methyl-4-chloropiperidine in an inert solvent such as tetrahydrofuran. Other organometallic reagents known in the art may also be used; for example, N-methyl-4-lithiopiperidine. The reaction may be conducted at or below room temperature (e.g., about -15 to about 25°C); however, the reaction mixture may be refluxed if necessary. Quenching the reaction with a mild acid (such as aqueous hydrochloric acid) or water produces an alcohol of Formula VIII. The Grignard reagent may be prepared from the corresponding halo derivative using methods well known in the art.

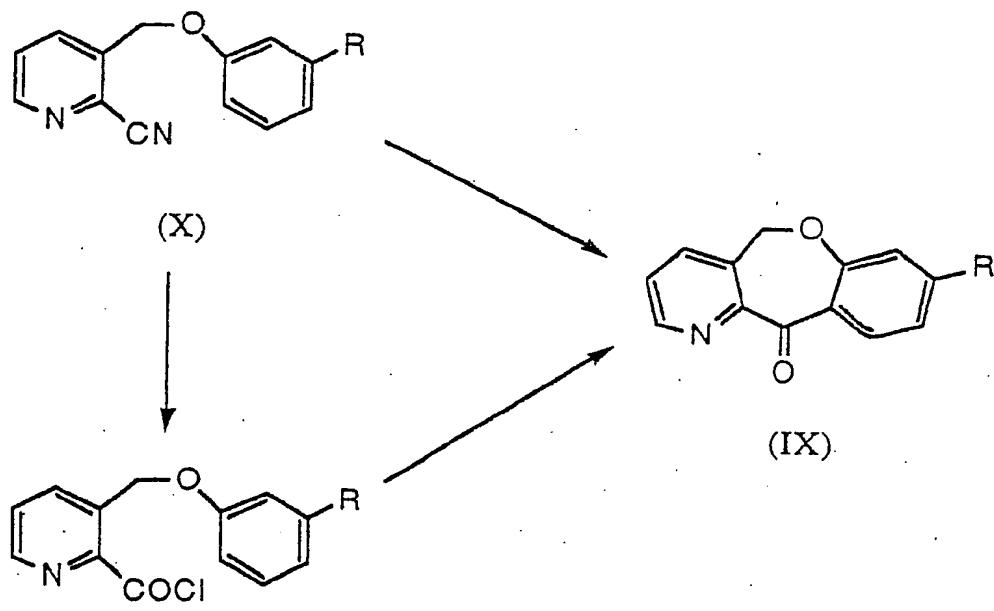


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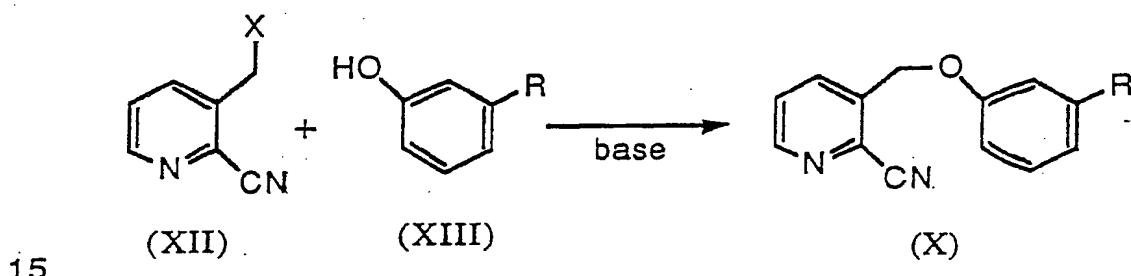
(c) There are many methods known in the art that may be employed for the preparation of substituted ketones of Formula IX. For example, the ketones of Formula IX can be prepared via an

- 17 -

intramolecular cyclization of the corresponding nitrile of Formula X. This transformation may be accomplished using a strong acid, such as trifluoromethanesulfonic acid, at room temperature. Other temperatures may be employed, for example about -15 to about 100°C. Other acids which may be used include sulfuric acid or polyphosphoric acid. The addition of water or aqueous acid to the reaction mixture is necessary following the cyclization in order to effect hydrolysis of the resultant imine to the corresponding ketone of Formula IX. Alternatively, an intramolecular Friedel-Crafts acylation of the acid chloride of Formula XI would also provide the desired ketone of Formula IX. The reaction may be carried out under usual Friedel-Crafts conditions in an inert solvent and in the presence of a Lewis acid such as aluminum chloride. The necessary acid chloride of Formula XI may be obtained from the nitrile of Formula X by the nitrile's hydrolysis to the corresponding carboxylic acid with aqueous acid (e.g., aqueous hydrochloric acid with heating) followed by its conversion to the acid chloride of Formula XI by standard conditions (e.g., thionyl chloride or oxalyl chloride) well known to those skilled in the art.



(d) Compounds of Formula X can generally be prepared by reaction of an alkyl halide of Formula XII (wherein X is a halogen or other leaving group known in the art) with a phenol of Formula XIII. Those skilled in the art will appreciate that these displacements may be conducted at a variety of temperatures (usually between room temperature and 100°C) in the presence of a base and a suitable polar solvent. Representative examples of bases which may be used to remove the phenolic proton include cesium carbonate (wherein acetone may be used as the polar solvent) or sodium hydride (wherein tetrahydrofuran may be used as the polar solvent). In this method, the alkyl halide of Formula XII may be coupled to the phenol of Formula XIII to produce the nitrile of Formula X.

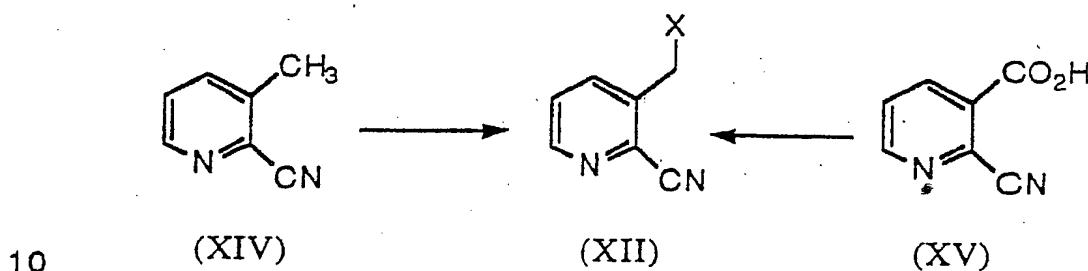


Alternatively, if X is a hydroxyl group in the compound of Formula XII then it may be coupled with the phenol of Formula XIII using known in the art Mitsunobe conditions. For example, the 20 compounds of Formulas XII and XIII may be coupled to produce a compound of Formula X using triphenyl phosphine and diethyl azadicarboxylate in an inert dry solvent such as tetrahydrofuran. The reaction may usually be conducted at or below 0°C (e.g., about -15 to about 0°C); however, the reaction may also be heated to reflux.

25 (e) The required alkyl halide of Formula XII (X is halogen) can be obtained from the corresponding 3-methyl-2-cyanopyridine of Formula XIV. Halogenation of the compound of Formula XIV can best be accomplished under free radical conditions using, for example, N-bromosuccinamide to provide the bromide (X =

- 19 -

Br), or sulfonyl chloride to provide the chloride (X = Cl). These reactions are carried out in an inert solvent, such as carbon tetrachloride, either in the presence of an initiator, such as aza(bis)isobutyronitrile (ABIN), and heat (about > 50°C) or light. Alternatively, a compound of Formula XII, 5 wherein X is a hydroxyl group, may be obtained from the corresponding carboxylic acid of Formula XV using reductive conditions which do not result in reduction of the cyano group (e.g., diborane in tetrahydrofuran) as is well known in the art.



10 In the above processes, it is sometimes desirable and/or necessary to protect certain groups during the reactions. Conventional protecting groups are operable as described in Greene, T.W., "Protective 15 Groups In Organic Synthesis," John Wiley & Sons, New York, 1981, the disclosure of which is incorporated herein by reference thereto. After the reaction or reactions, the protecting groups may be removed by standard procedures.

20 The compounds of the invention possess platelet-activating factor ("PAF") and histamine antagonistic properties. The compounds of the invention are, therefore, useful when PAF and/or histamine are factors in the disease or disorder. This includes allergic diseases such as asthma, respiratory distress syndrome, urticaria and inflammatory diseases such as rheumatoid arthritis and osteo-arthritis. 25 For example, PAF is an important mediator of such processes as platelet aggregation, smooth muscle contraction (especially in lung tissue), vascular permeability and neutrophil activation. Recent evidence

- 20 -

implicates PAF as an underlying factor involved in airway hyperreactivity.

The PAF antagonistic properties of these compounds may be demonstrated by use of standard pharmacological testing procedures as described below. These test procedures are standard tests used to determine PAF antagonistic activity and to evaluate the usefulness of said compounds for counteracting the biological effects of PAF. The *in vitro* assay is a simple screening test, while the *in vivo* test mimics clinical use of PAF antagonists to provide data which simulates clinical use of the compounds described herein.

A. IN VITRO STUDIES

Platelet Aggregation Assay

15 Platelet-activating factor (PAF) causes aggregation of platelets by a receptor-mediated mechanism. Therefore, PAF-induced platelet aggregation provides a simple and convenient assay to screen compounds for PAF antagonism.

20 Human blood (50 mL) was collected from healthy male donors in an anticoagulant solution (5 mL) containing sodium citrate (3.8%) and dextrose (2%). Blood was centrifuged at 110 x g for 15 min. and the supernatant platelet-rich plasma (PRP) carefully transferred into a polypropylene tube. Platelet-poor-plasma (PPP) was prepared by 25 centrifuging PRP at 12,000 x g for 2 min. (Beckman Microfuge B). PRP was used within 3 hr. of drawing the blood.

PAF was dissolved in chloroform:methanol (1:1, v/v) at a concentration of 2 mg/mL and stored at -70°C. An aliquot of this solution was transferred to a polypropylene tube and dried under a flow of 30 nitrogen gas. To the dried sample was added Hepes-saline-BSA (BSA = bovine serum albumen) buffer (25 mM Hepes, pH 7.4, 1254 mM NaCl, 0.7 mM MgCl₂ and 0.1% BSA) to obtain a 1 mM solution and sonicated for 5 min. in a bath sonicator. This stock solution was further diluted to appropriate concentrations in Hepes-saline-BSA buffer. Collagen

- 21 -

(Sigma) and adenosine diphosphate (ADP) (Sigma) were purchased as solutions. Test compounds were initially dissolved in dimethyl sulfoxide (DMSO) at a concentration of 50 mM and then further diluted in Hepes-saline-BSA buffer to achieve appropriate concentrations.

5 When an aggregating agent such as PAF is added to PRP, platelets aggregate. An aggregometer quantifies this aggregation by measuring and comparing light (infra-red) transmission through PPP and PRP. Aggregation assays were performed using a dual-channel aggregometer (Model 440, Chrono-Log Corp., Havertown, PA). PRP (0.45 mL) in aggregometer cuvettes was continually stirred (37°C).
10 Solutions (50 µL) of test compounds or vehicle were added to the PRP and, after incubation for 2 min., 10-15 µL aliquots of PAF solution were added to achieve a final concentration of 1.5×10^{-8} M. In different experiments the aggregatory response was kept within a set limit by varying the concentration of PAF. Incubations were continued until the increase in light transmission reached a maximum (usually 2 min.). This increase in light transmission reflecting platelet aggregation is transmitted to a computer by the Chrono-Log model 810 AGGRO/LINK interface. The AGGRO/LINK calculates the slope of transmission change, thus
15 providing the rate of aggregation. Values for inhibition were calculated by comparing rates of aggregation obtained in the absence and the presence of the compound. For each experiment, a standard PAF antagonist such as 8-chloro-6,11-dihydro-11-(1-acetyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine was used as a
20 positive control.
25

Compounds that inhibit PAF-induced aggregation were tested against several other aggregating agents including collagen (0.2 mg/mL) and ADP (2 µM). Compounds showing no activity against these latter agents were considered to be specific PAF antagonists. Results
30 are shown in TABLE 1 below.

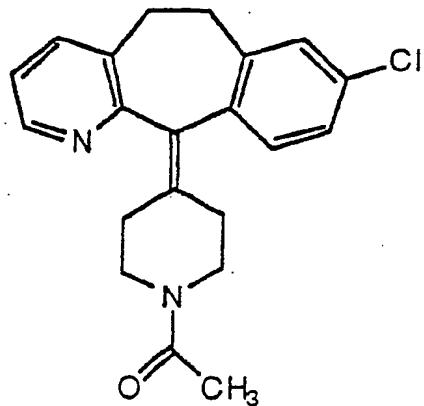
B. In Vivo Studies: Agonist-Induced ResponsesSpasmogen-Induced Bronchospasm in Guinea Pigs

5 Male Hartley guinea pigs (450-550 g) were obtained from Charles River Breeding Laboratories. The animals were fasted overnight and the following day were anesthetized with 0.9 mL/kg i.p. of dialurethane (containing 0.1 g/mL diallylbarbituric acid, 0.4 g/mL ethylurea and 0.4 g/mL urethane). The left jugular vein was cannulated
10 for the administration of compounds. The trachea was cannulated and the animals were ventilated by a rodent respirator at 55 strokes/min. with a stroke volume of 4 mL. A side arm to the tracheal cannula was connected to a pressure transducer to obtain a continuous measure of inflation pressure. Bronchoconstriction was measured as the percent
15 increase in inflation pressure that peaked within 5 min. after challenge with spasmogen. The animals were challenged i.v. with either histamine (10 μ g/kg) or PAF (0.4 μ g/kg in isotonic saline containing 0.25% BSA). Each animal was challenged with only a single spasmogen. The effect
20 of a compound on the bronchospasm is expressed as a percent inhibition of the increase in inflation pressure compared to the increase in a control group. Results are shown in Table 1 below.

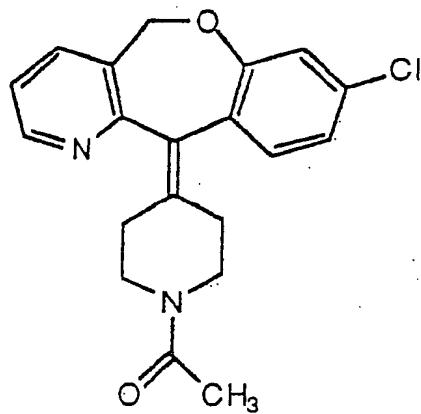
In Table 1 the column "No." represents "Compound Numbers" and Compound Numbers 1 to 4 in Table 1 refer to:

25 (a) Compound No. 1 is disclosed in WO 88/03138, discussed above, and has the structure:

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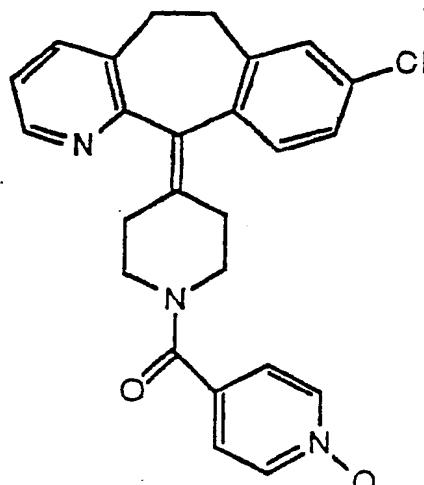


5 (b) Compound No. 2 is disclosed in
WO 89/10369, discussed above, and has the
structure:



10 (c) Compound No. 3 is disclosed in
WO 90/13548, discussed above, and has the
structure:

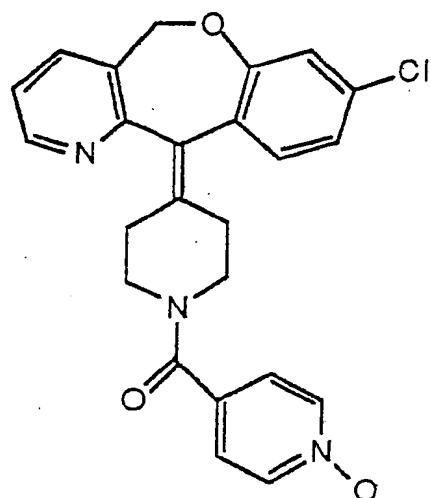
- 24 -



; and

(d) Compound No. 4, a compound of the invention, has the structure:

5



- 25 -

TABLE 1

No.	PAF Antagonism (in vitro) IC ₅₀ (μM)	Agonist Bronchospasm (in vivo)-Oral			
		PAF		Histamine	
		<u>Dose</u> (mg/kg)	<u>Inhibition</u> (%)	<u>Dose</u> (mg/kg)	<u>Inhibition</u> (%)
1	0.6	3	3 ^a	3	49 ^a
		15	32 ^b	15	100 ^b
2	6	10	27 ^a	--	--
3	0.2	3	93 ^a	3	37 ^a
		5	12 ^b	5	33 ^b
		15	13 ^d	15	64 ^d
4	0.4	3	76 ^a	3	46 ^a
		10	94 ^c	10	73 ^c
		10	55 ^d	10	95 ^d

a % inhibition 2 hours after drug
b % inhibition 8 hours after drug
c % inhibition 6 hours after drug
d % inhibition 16 hours after drug

The data in Table 1 demonstrate that the compounds of
5 this invention (e.g., Compound No. 4 in Table 1):

- (1) have activity as antagonists of PAF and histamine;

- 26 -

- (2) have anti-^{ASP} and anti-histamine activities that are more equipotent than compounds known in the art as dual antagonists of PAF and histamine; and
- 5 (3) have a longer duration of the anti-PAF activity than compounds known in the art as dual antagonists of PAF and histamine.

Thus, the compounds of this invention are more equipotent and have a longer lasting (longer duration) activity as antagonists of PAF and 10 histamine than compounds known in the art as dual antagonists of PAF and histamine.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations 15 include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as 20 solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized 25 molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example there may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for 30 intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

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Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

5 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

10 Preferably the compound is administered orally. Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

15 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 500 mg, according to the particular application. The appropriate dosage can be determined by comparing the activity of the compound with the activity of a known antihistaminic
20 compound such as 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which compound is disclosed in U.S. Patent No. 4,282,233.

25 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For
30 convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending

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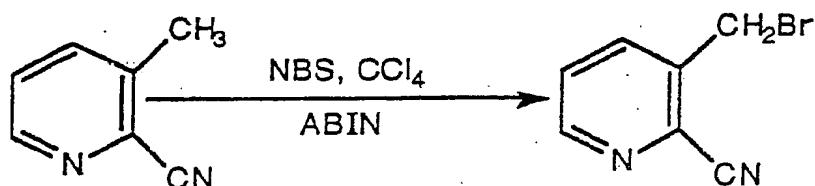
clinician considers as age, condition and size of the patient as well as severity of symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 1500 mg/day, preferably 10 to 750 mg/day, in two to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered within this dosage range.

The following examples are intended to illustrate, but not to limit, the present invention.

10

PREPARATIVE EXAMPLE

A. 2-Cyano-3-(bromomethyl)pyridine



15

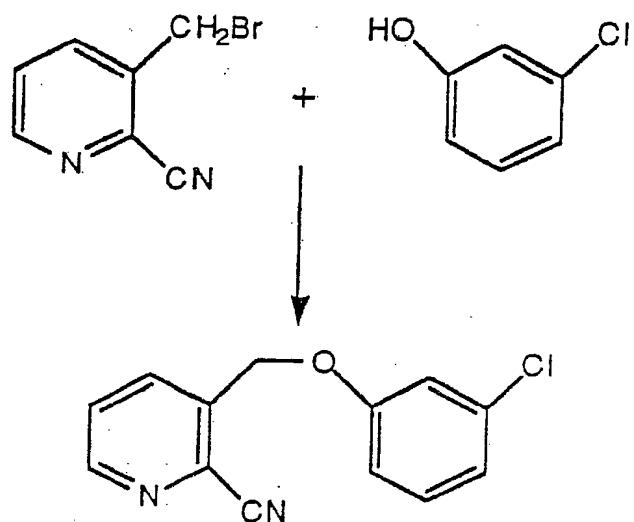
Combine 2-cyano-3-methylpyridine (11.8g), N-bromosuccinimide (NBS) (26.8g, 1.5 eq.) and aza(bis)isobutyronitrile (ABIN) (180 mg) in dry CCl_4 (300 mL). Reflux the mixture overnight.

20 Pour the mixture into water, basify with NaOH and extract with CH_2Cl_2 . Wash the organic portion with water, dry (Na_2SO_4), filter and concentrate to obtain a liquid. Chromatograph the product, eluting with 30% diethyl ether in hexanes. Combine the appropriate fractions to obtain the mono bromo compound (5.01 g) as a yellowish solid: m.p. 41.5-42.5°C.

25

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B. 2-Cyano-3-(3-Chlorophenoxy)methylpyridine

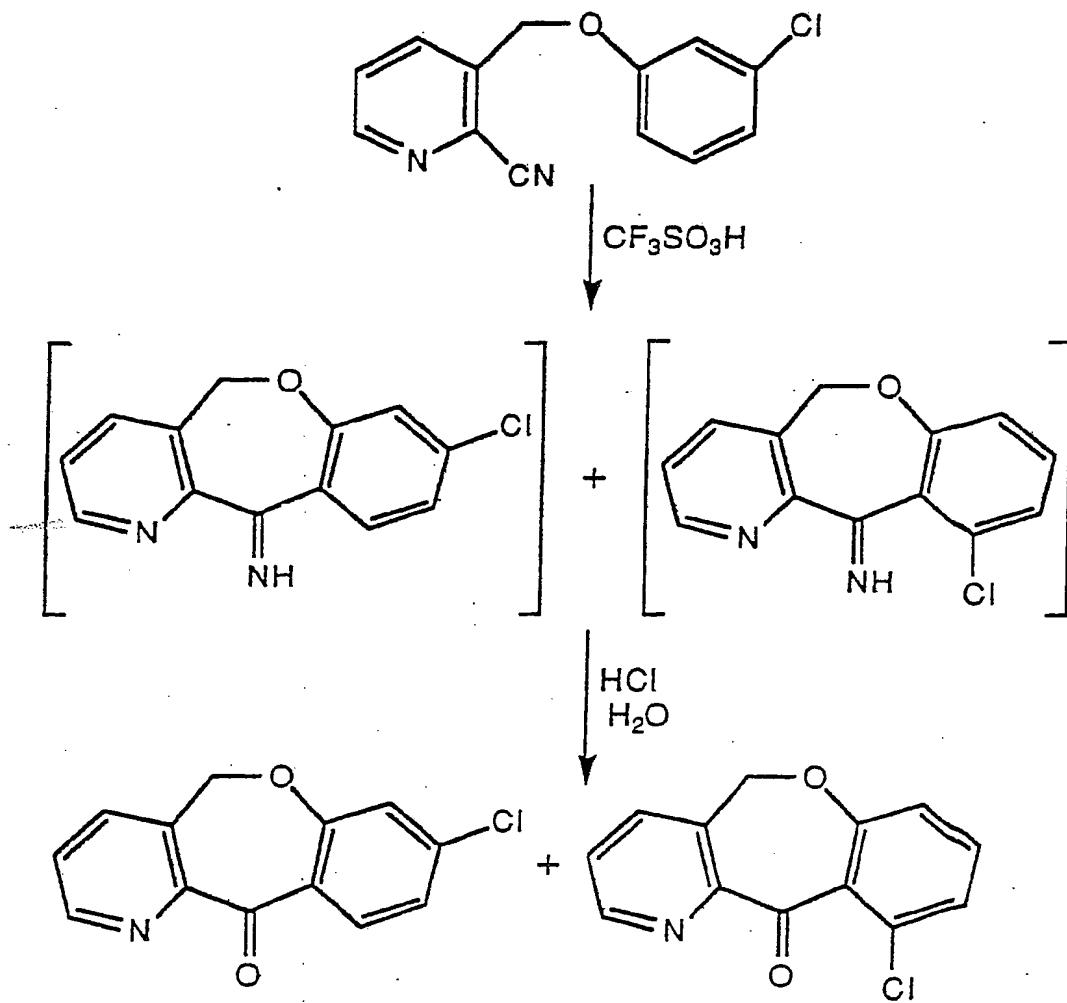


5. Stir a solution of the title compound of part A above (0.71 g, 3.6 mmol), NaI (54 mg, 0.1 eq) and Cs₂CO₃ (1.17 g, 1.0 eq) in dry acetone (17 mL, dried over MgSO₄) at room temperature for 5 minutes, then add 3-chlorophenol (463 mg) via a syringe.
Reflux over an oil bath for 4.5 hours.

10. Filter and wash the filtrate with dry acetone. Concentrate the filtrate, suspend in diethyl ether, and refilter to obtain a brown solid which is the title compound in crude form. Triturate with pentane, and resuspend in diisopropyl ether (40 mL) with charcoal, and heat on a steam bath.

15. Filter and evaporate the solvent to obtain the title compound, which crystallizes to form a white solid (640 mg); m.p. 70-72°C.

- 30 -

C. 8-Chloro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin-11-one

5 Stir the title compound from part B above (6.1 g) in $\text{CF}_3\text{SO}_3\text{H}$ (60 mL) at room temperature for 3 hours. Upon completion, quench with H_2O and conc. HCl (30%) and continue stirring for 0.5 hours.

10 Warm to 35°C for 0.5 hours. Basify with NaOH (25%) and extract with CH_2Cl_2 (2X). Wash with brine (2X), filter and dry over Na_2SO_4 , and concentrate in vacuo to afford a semi-solid.

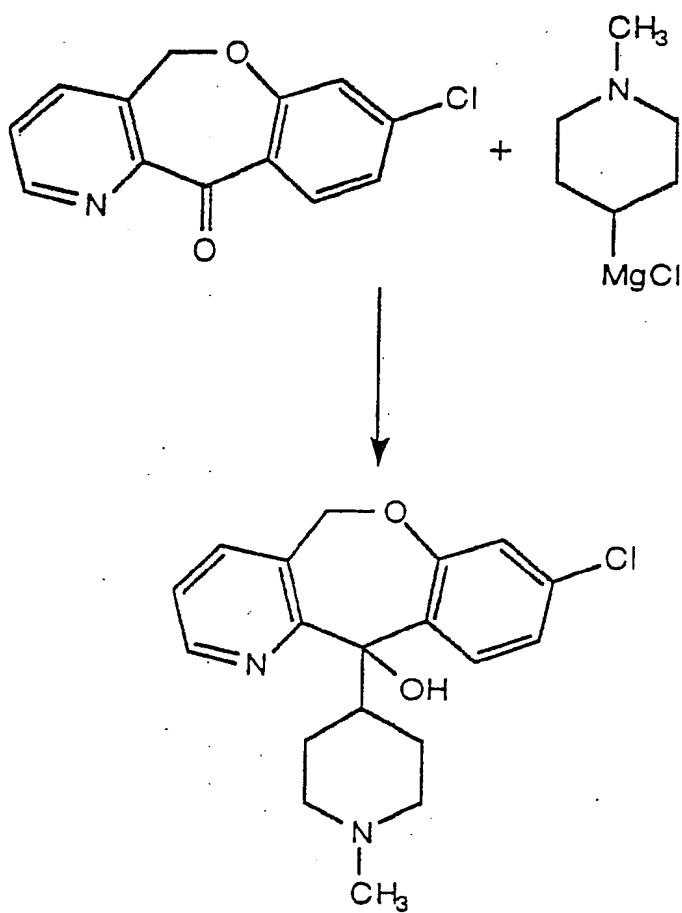
Triturate the resulting semisolid (6.35 g) with diisopropyl ether and separate the isomers via flash chromatography (30% ethyl

- 31 -

acetate in hexanes). Combine the appropriate fractions to obtain the title compound as a solid (4.902 g): m.p. 139.5-140.5°C, and the 10-chloro compound as a solid (498 mg): m.p. 100-102°C.

5

D. 1-Methyl-4-(8-chloro-11-hydroxy-5,11-dihydro[1]benzoxepino[4,3-b]pyridinyl)piperidine



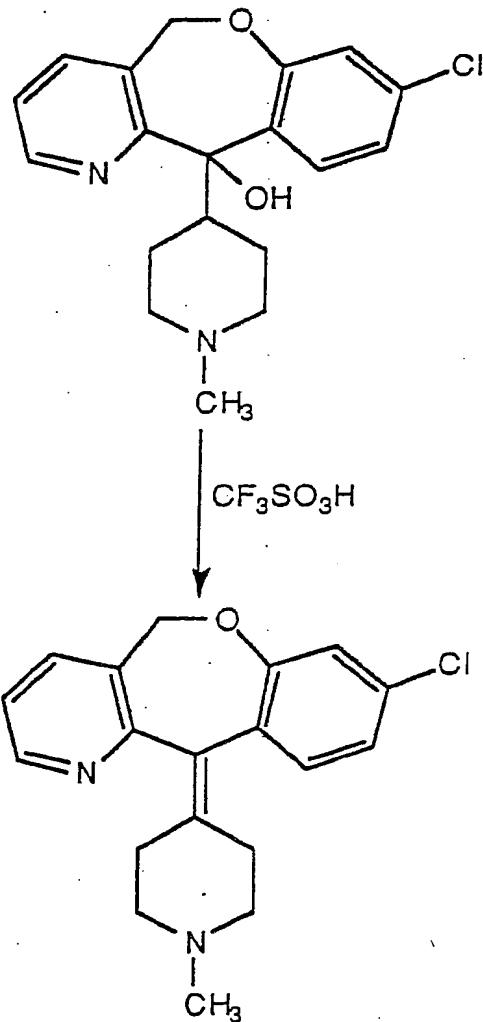
10

Slowly add the Grignard reagent (11.9 mL, 1.2 M) derived from N-methyl-4-chloropiperidine to a stirred solution of the title compound from part C above (3.47 g) in dry tetrahydrofuran (37 mL). Stir the solution for 30 minutes after the addition.

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Quench the reaction with ice and NH₄Cl. Extract the solution with CH₂Cl₂ (2X), dry, filter and concentrate to obtain the title compound. Chromatograph the product on silica gel eluting with 5 → 7.5% CH₃OH/NH₃ in CH₂Cl₂ to obtain the title compound as a glass (2.56 g): MS (EI) m/e 344 (M⁺).

E. 1-Methyl-4-(8-chloro-5,11-dihydro[1]benzoxepin[4,3-*b*]pyridin-11-ylidene) piperidine



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Stir the title compound from part D above (934 mg) in CF₃SO₃H (20 mL) at room temperature for 15 minutes. Raise temperature to 45°C on an oil bath and maintain for 1.25 hours. Cool to room temperature and pour the mixture into ice water. Basify with dilute NaOH, and extract with CH₂Cl₂ (2X). Wash with brine (1X) and dry over Na₂SO₄ to obtain the title compound as a brown glass.

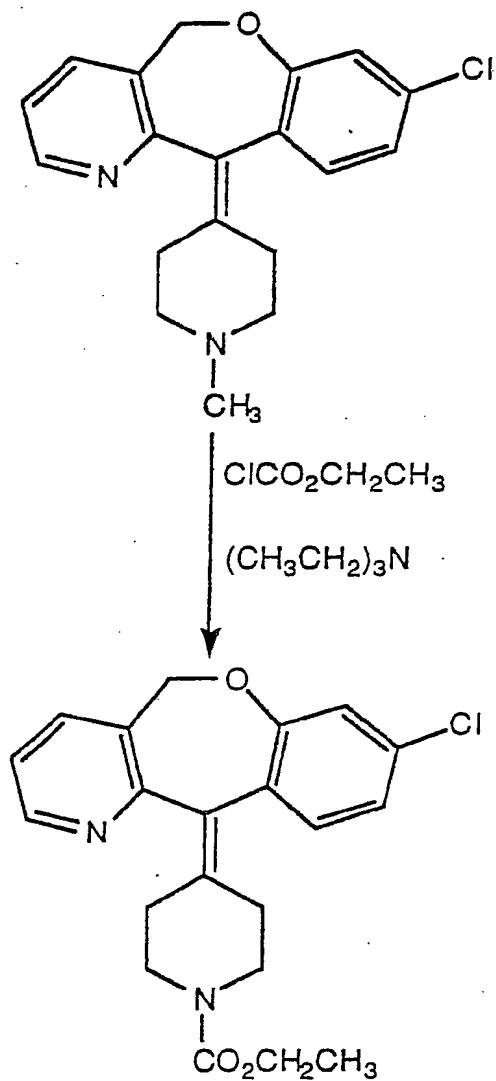
5 Purify by combining with charcoal in ethyl acetate, then filter and remove solvent to obtain a yellowish brown solid.

Recrystallize from ethyl acetate and diisopropyl ether to obtain the title compound as an off-white solid (540 mg): m.p. 168-170°C.

10

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E. 1-Ethoxycarbonyl-4-(8-chloro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin-11-ylidene)piperidine



5

Dissolve the title compound from part E above (474 mg, 1.45 mmol) in toluene (10 mL) and add triethylamine (0.656 mL). Warm and maintain the reaction at 80-85°C and slowly add ethyl chloroformate (1.242 mL). Maintain the reaction at 80-85°C while stirring for 3 hours.

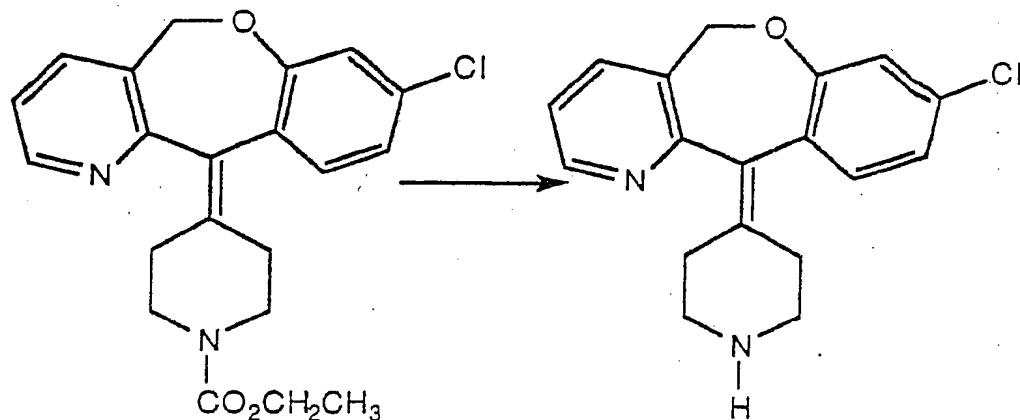
- 35 -

Quench the reaction with H_2O and extract with ethyl acetate (2 X 100 mL). Wash with brine, separate and dry over Na_2SO_4 . Remove the solvent and purify via flash chromatograph, eluting with 40 → 60% ethyl acetate in hexanes to yield the title compound as an off-white solid, which may be purified by trituration with pentane and diisopropyl ether to render a powder (428 mg): m.p. 118-120°C.

5 off-white solid, which may be purified by trituration with pentane and diisopropyl ether to render a powder (428 mg): m.p. 118-120°C.

G. 4-(8-Chloro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin-11-ylidene)piperidine

10



Dissolve the title compound from part F above (333.8 mg) in ethanol (5 mL) and add 14% aqueous KOH. Reflux under an argon atmosphere for 19 hours.

15

Quench the reaction with H_2O and extract with CH_2Cl_2 (3 x 100 mL). Wash with brine (1 x 100 mL), dry over Na_2SO_4 and filter. Remove the solvent to yield a glassy off-white solid.

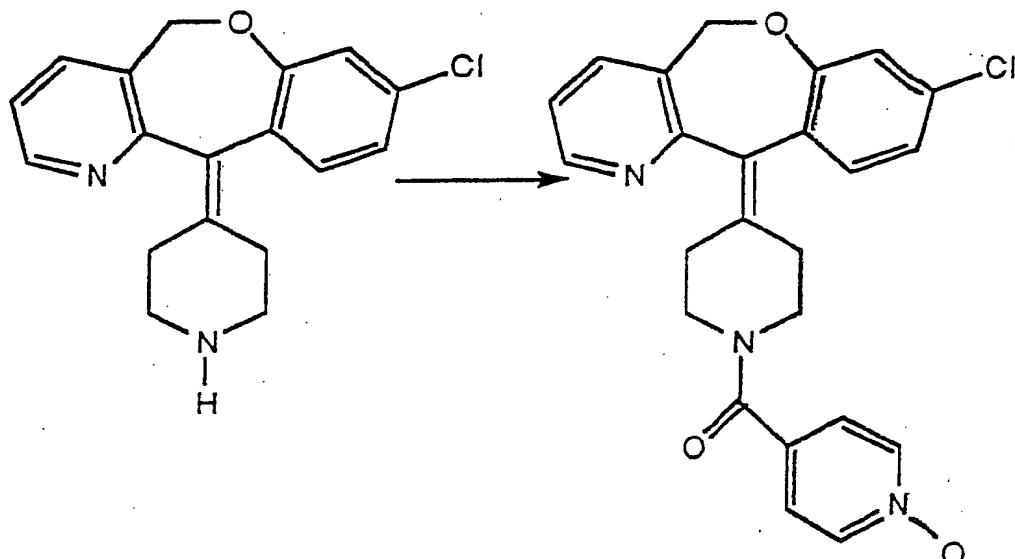
20 Recrystallize with ethyl acetate/diisopropyl ether to yield the title compound as a white powder (161.5 mg): m.p. 166-176°C (dec).

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EXAMPLE 1

4-(8-Chloro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin-11-ylidene)-1-(4-pyridinylcarbonyl)piperidine N¹-oxide

5



Add isonicotinic acid N-oxide (0.90 g, 6.47 mmole) to 8-chloro-5,11-dihydro-11-(4-piperidinylidene)[1]benzoxepino-[4,3-b]pyridine (1.19 g, 3.80 mmole) in dichloromethane (25 mL) at 0°C under a nitrogen atmosphere. Add 1-hydroxybenzotriazole hydrate (0.87 g, 6.47 mmole) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.24 g, 6.47 mmole). Warm the reaction mixture up slowly, and stir for 22 hours at room temperature. Add 1 N NaOH (40 mL), and separate layers. Extract the aqueous portion with dichloromethane (2x40 mL). Wash the combined organic portions with saturated NaCl, dry with MgSO₄, filter, and concentrate in vacuo. Dissolve the foamy solid in dichloromethane, and chromatograph on silica gel, eluting with 7% methanol in dichloromethane, then 10% methanol in dichloromethane. Combine the appropriate fractions, and concentrate under reduced pressure to give a beige foamy solid. Dissolve the solid in ethanol, and add 1.1 equivalents of 20 wt % HCl in

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ethanol. Rotoevaporate to remove the solvent. Dry the product (1.50 g) at room temperature under high vacuum (0.05 torr) for 16 hours to obtain the title compound as a tan powder, containing 3/4 mole ethanol and 1/4 mole water, with a melting range of 194-200°C.

5

The following are examples of pharmaceutical dosage forms which may contain a compound of the invention. As used herein, the term "active compound" is used to designate the compound 4-(8-Chloro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin-11-ylidene)-1-(4-pyridinylcarbonyl)piperidine N¹-oxide. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided, since any other compound of structural Formula I can be substituted into the pharmaceutical composition examples.

15

Pharmaceutical Dosage Form Examples

Example A

Tablets

<u>No.</u>	<u>Ingredient</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	TOTAL	300	700

20

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4") if needed. Dry the damp granules. Screen the dried 25 granules if needed and mix with Item No. 4 and mix for 10-15 minutes.

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Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

No.	<u>Ingredient</u>	<u>Example B</u>	
		<u>mg/tablet</u>	<u>mg/tablet</u>
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	TOTAL	250	700

Method of Manufacture

10 Mix Item Nos. 1, 2, and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

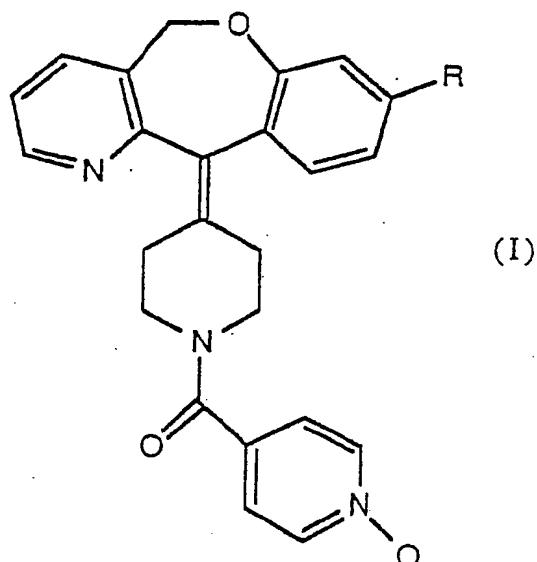
15 While the present invention has been described in connection with certain specific embodiments thereof, it will be evident to one of ordinary skill in the art that many alternatives, modifications and variations may be made. All such alternatives, modifications and variations are intended to be included within the spirit and scope of the invention.

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WHAT IS CLAIMED IS:

1. A compound of Formula I:



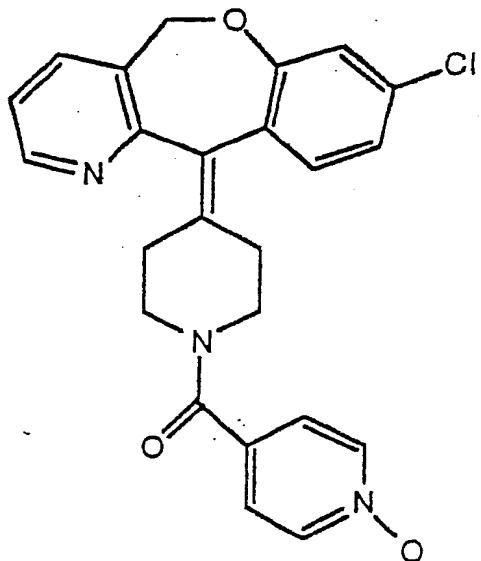
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10

or a pharmaceutically acceptable salt or solvate thereof, wherein R is selected from the group consisting of: H and halogen atoms, said halogen atoms being selected from the group consisting of: Cl, Br, F, and I.

- 40 -

2. A compound of the formula:



5 3. A pharmaceutical composition comprising a compound of either Claim 1 or Claim 2 in combination with a pharmaceutically acceptable carrier.

10 4. A method of treating asthma comprising administering to a mammal in need of such treatment an anti-asthmatic effective amount of a compound of either Claim 1 or Claim 2.

15 5. A method of treating allergy comprising administering to a mammal in need of such treatment an anti-allergic effective amount of a compound of either Claim 1 or Claim 2.

20 6. A method of treating inflammation comprising administering to a mammal in need of such treatment an anti-inflammatory effective amount of a compound of either Claim 1 or Claim 2.

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7. The use of a compound of either Claim 1 or Claim 2 for the manufacture of a medicament for use in treating asthma, allergy or inflammation.

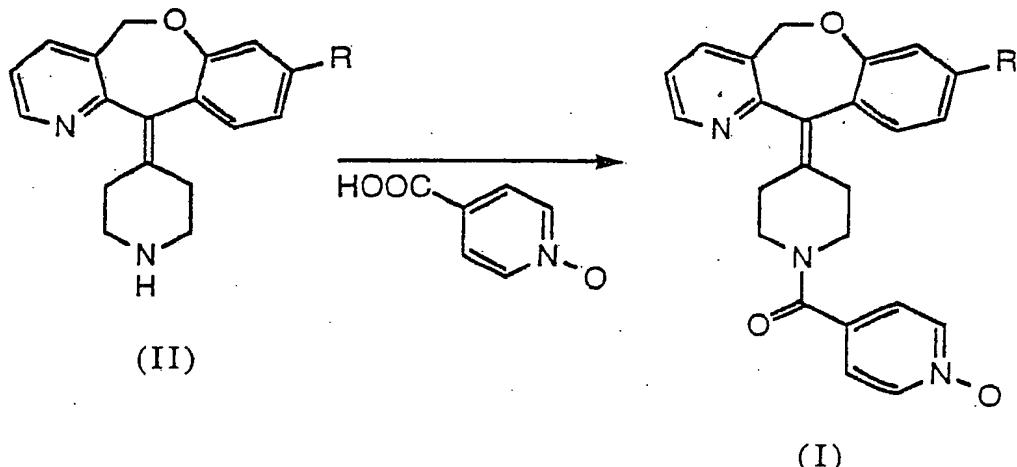
5 8. The use of a compound of either Claim 1 or Claim 2 for the treatment of asthma, allergy or inflammation.

9. A method of preparing a pharmaceutical composition comprising admixing a compound of either Claim 1 or 10 Claim 2 with a pharmaceutically acceptable carrier.

10. A process for preparing a compound of Claim 1 comprising:

(A)

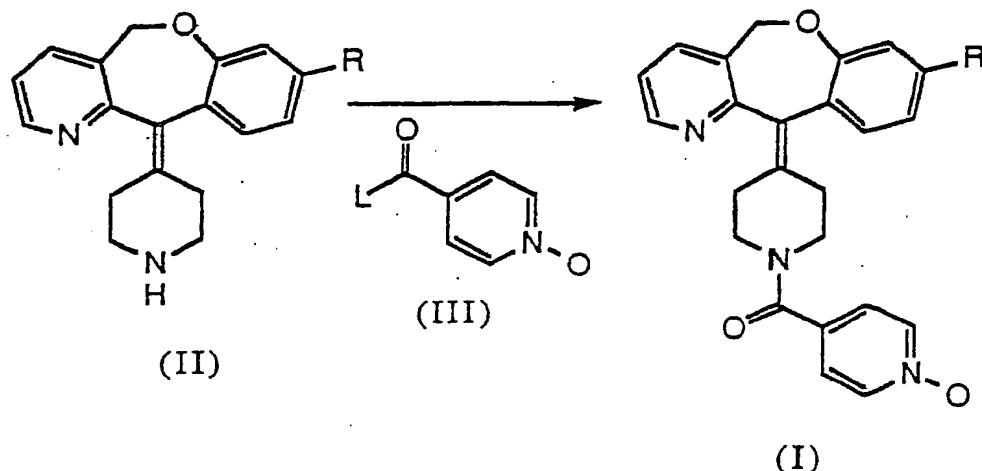
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coupling a compound of Formula II with isonicotinic acid N-oxide in the presence of a coupling agent;

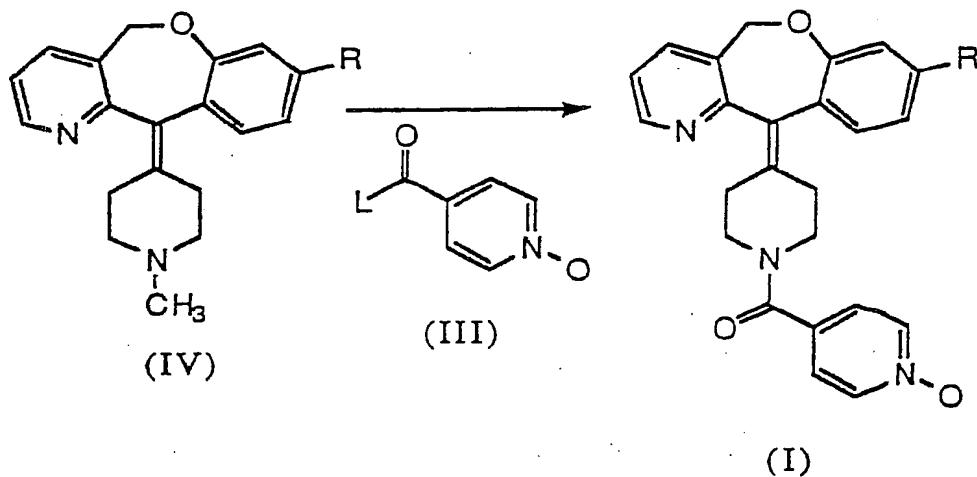
- 42 -

(B)



5 reacting a compound of Formula II with a compound of Formula III; or

(C)



10

reacting a compound of Formula IV with a compound of Formula III.

11 The process of Claim 10 wherein said compound of Formula I is the compound of Claim 2.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 92/04003

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. C1.5 C 07 D 491/044 A 61 K 31/44 // (C 07 D 491/044
C 07 D 313:00 C 07 D 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int. C1.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP, A, 0341860 (SCHERING CORP.) 15 November 1989, see claims 1,14 (cited in the application) ---	1,7
A	EP, A, 0396083 (SCHERING CORP.) 7 November 1990, see claims 1,18 ---	1,7
P,A	WO, A, 9200293 (SCHERING CORP.) 9 January 1992, see claims 1,41 -----	1,7

* Special categories of cited documents :¹⁰

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

19-08-1992

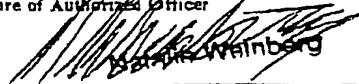
Date of Mailing of this International Search Report

21.09.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer


BOB-ME Wahlberg

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 4-6 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the composition/compound.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest

No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 9204003
SA 60890

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/09/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0341860	15-11-89	AU-A-	3734489	24-11-89
		EP-A-	0411048	06-02-91
		JP-T-	3504012	05-09-91
		WO-A-	8910369	02-11-89
		US-A-	5104876	14-04-92
EP-A- 0396083	07-11-90	US-A-	5089496	18-02-92
		AU-A-	5642090	29-11-90
		EP-A-	0471750	26-02-92
		WO-A-	9013548	15-11-90
WO-A- 9200293	09-01-92	AU-A-	8225291	23-01-92